Towards Mucosal Application of infliximab in the Therapy of Enterocolitis (TOMATE): a proof of concept study

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Summary

Introduction:
Intravenous or subcutaneous administered antibodies against anti-TNF alpha are highly efficacious in the treatment of inflammatory bowel disease (IBD). Intravenous administration of Infliximab (IFX) in Crohn’s disease (CD) can induce remission and mucosal healing of ulcers. However, intravenous administration of IFX is associated with high costs, systemic immunosuppression, infusion reactions and the development of antibodies to IFX (ATI). Therefore we developed an oral formulation of IFX and want to examine if oral IFX can induce clinical remission and mucosal healing.

Aim:
To evaluate the efficacy and safety of orally administered ColoPulse IFX tablets targeted to the ileo-colonic region in CD patients.

Study design:
Multicentre, open label, observational, pilot study.

Study population:
Patients with active ileal or ileo-colonic CD.

Intervention:
Daily administration of ColoPulse IFX tablets instead intravenously administered IFX. The total administered oral dose is the same as the intravenous dose.

Primary study endpoints:
Efficacy of oral IFX biosimilar CT-P13 in ColoPulse tablets to induce clinical remission based on CDAI score of < 150 at wk 18.
Secondary study endpoints

- Clinical response: CDAI reduction from baseline of ≥ 100 points
- Endoscopic remission: for patient with Simple Endoscopic Score for Crohn’s Disease (SES-CD) (see table 1) of 3 a drop to 0 and for patient with SES-CD > 3 a drop ≤ 3
- Endoscopic response: proportion of subjects with SES-CD decrease from baseline of ≥ 50 % at Week 18 but not meeting criteria for endoscopic remission.
- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points at Week 18
- Number of patients with reduction in prednisolone dose below 10 mg or budesonide dose below 6 mg or off steroids at week 18.
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥ 10% at Week 18
- Improvement in faecal calprotectin and C-reactive-protein (CRP) level.
- Non-remitter: Subjects who do not achieve clinical remission at week 18
- Non responder: Subjects who do not achieve clinical response at Week 18.

Other secondary endpoints

- IFX trough level at week 8 and 18
- Proportion of patients with development of antibodies to IFX CT-P13 at week 18
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥ 10% at Week 18
- Improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) scores
Introduction

Crohn’s Disease (CD) is a chronic inflammatory bowel disease (IBD) that is characterised by a transmural inflammation of the gastrointestinal tract, with a predilected involvement of the terminal ileum. Although the exact etiology of CD remains to be elucidated, a widely accepted hypothesis is that ubiquitous, commensal intestinal bacteria trigger an aberrant, overactive, and ongoing mucosal immune response that mediates intestinal tissue damage in genetically susceptible individuals. Treatment options for CD depend on site of inflammation, disease activity, and patient’s response. Treatment is divided in an induction phase in order to stop the mucosal inflammation and heal the mucosal lesions and the maintenance phase in order to maintain this non-inflammatory state and prevent complications. Tumor necrosis factor-alpha (TNF-alpha) is an important cytokine involved in the mucosal inflammation since it induces, maintains and amplifies the inflammation through several mechanisms, such as the up-regulation of endothelial adhesion molecules and the activation and recruitment of immune cells.

Infliximab (IFX), a chimeric mouse-human monoclonal antibody against TNF alpha, is efficacious in the treatment of CD not responding to conventional therapy. IFX is effective in inducting and maintaining remission and of both luminal and fistulising CD. IFX is administered intravenously at doses based on body weight and fixed intervals. This gives rise to certain disadvantages. First, patients need to visit the hospital for the treatment and the infusion need to be prepared by trained personnel. Furthermore, the patient gets punctured and receives the infusion over a period of time at which monitoring by trained personnel takes place.

Moreover, inherently linked to infusion therapy, acute and late-onset infusion reactions can occur. Additionally, substantial side effects are expected as TNF alpha is an endogenous mediator and systemic administration of IFX will cause systemic immunosuppression. Finally, antibody towards IFX (ATI) could develop leading to an increase in side effects or loss of response to IFX therapy. These disadvantages have a negative impact on disease burden and health care cost as well as patient-friendliness. The majority of these disadvantages could be eliminated if IFX is administered orally, targeting the inflamed region, and inducing a local, anti-inflammatory effect.

The ColoPulse technology is a coating technology which consist of a pH-sensitive polymer in which a superdisintegrant is incorporated in the coating matrix. This coating was specifically developed to target the ileo-colonic region in humans and is characterized by fast and site-specific drug targeting. ColoPulse capsules and tablets has been studied in targeting the ileo-colonic region in healthy subjects as well as CD patients and food and time of food intake does not affect coating performance. Furthermore, we have shown that IFX compounded in ColoPulse tablets is feasible and stable. The objective of this proof of concept study is to treat patients with active ileo-colonic CD with orally administered ColoPulse IFX tablets instead of intravenously administrated IFX. Efficacy and safety will be investigated as well as oral IFX pharmacokinetics and the development of ATI formation after oral IFX treatment.
Rationale and Justification of route of administration and dosage

As outlined above, orally administered IFX has several advantages over systemically administered IFX in view of health costs and burden and patient friendliness. Besides these practical and economic considerations, systemically administered IFX can induce the development of ATI. The formation of ATI in CD patients is associated with infusion reaction, resulting in a two-fold risk of acute infusion reaction whereas they have a six-fold risk of developing serious acute infusion reaction.\textsuperscript{11,12,22-25} Furthermore, several studies demonstrated a correlation between IFX drug concentrations, the presence of ATI, and clinical outcome. Episodic IFX treatment in patients with CD has been associated with a higher rate of ATI as compared with scheduled maintenance therapy. Patients on IFX therapy who develop ATI have a threefold higher increased risk of loss of response to therapy compared to those who do not develop ATI’s.\textsuperscript{12,26} In addition, ATI are associated with an increased clearance of IFX, which necessitates more frequent and/or higher dosing of IFX.\textsuperscript{27} The development of ATI in turn may increase health costs and burden and decrease quality of life for loss of response generally leads to intensifying the treatment and patient monitoring and an increase of disease symptoms, respectively. It is expected that oral IFX therapy does not result in substantial systemic exposure and therefore no development of ATI. Studies have shown that tissue IFX concentration correlates with a better and sustained response in CD\textsuperscript{28} and that IFX exerts its effect at least partly by local anti-inflammatory and immunomodulatory effects in the bowel.\textsuperscript{29} Additionally, eight open-label, uncontrolled pilot clinical trials have shown that the local administration of IFX in postoperative recurrent\textsuperscript{30} symptomatic isolated intestinal lesions,\textsuperscript{31} fistulising\textsuperscript{32-34} or stricturing\textsuperscript{35,36} CD is encouraging, ameliorates symptoms, and can be an effective treatment option for patients not responding to conventional therapy. For some patients, local administered IFX induces complete remission, even after a follow-up period of 30-40 months.\textsuperscript{31-33} Furthermore, no serious adverse events were observed during all eight studies. Moreover, in two of these studies patients were included that did not respond to systemically administered IFX and showed a clinical response to local administration of IFX.\textsuperscript{32,36} In another study, no ATI were developed during 6-month follow-up. Table 2 summarizes these eight studies. The administered dose in all studies was lower than the conventional doses, which in general ranges from 5-10 mg/kg every 2 (induction phase) to 8 (maintenance) weeks. However, no rational oral dose can be deduced from these studies as the IFX was injected directly into the inflamed areas and oral ileo-colonic-targeted IFX is a less direct manner to target these areas. Oral treatment eliminates the necessity to administer IFX directly with a syringe in the inflamed area during a colonoscopy or perianal examination. It is an easier, less laborious, and patient friendlier manner to locally target the inflammation, which can be performed solely by the patient. Furthermore, daily oral IFX treatment ensures a continuous exposure of the inflamed ileo-colonic mucosa to IFX and presumably eliminates systemic exposure, which may result in fewer side effects. A major disadvantage of oral IFX treatment is that there is no data with
Table 2. Summary of eight studies that investigated the applicability and feasibility of local administered IFX.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease location</th>
<th>N</th>
<th>Dosage</th>
<th>Duration</th>
<th>Follow-up</th>
<th>Effective in</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poggioli et al. (18)</td>
<td>Fistulizing, perianal Disease</td>
<td>15</td>
<td>15-21 mg</td>
<td>6-12x every 4 weeks</td>
<td>Mean 18.2 (3-30) months</td>
<td>10/15 healed</td>
<td>In combination with surgical treatment</td>
</tr>
<tr>
<td>Biancone et al. (14)</td>
<td>Localized recurrence after ileal or ileo-colonic resection</td>
<td>8</td>
<td>8-60 mg</td>
<td>1-2 x injections 2-4 weeks apart</td>
<td>Median 20 (14-21) months</td>
<td>3/8 improved endoscopic score; 7/8 reduced number and extent of lesions</td>
<td>No strictures/fibrosis at site of injection were observed</td>
</tr>
<tr>
<td>Asteria et al. (17)</td>
<td>Perianal fistulas</td>
<td>11</td>
<td>20 mg</td>
<td>3-5x every 4 weeks</td>
<td>Mean 10.5 (7-18) month</td>
<td>8/11 improved; 4/11 achieved remission</td>
<td>Health-related quality of life improved in patients in who responded</td>
</tr>
<tr>
<td>Alessandroni et al. (16)</td>
<td>Perianal fistulas</td>
<td>12</td>
<td>20-25 mg</td>
<td>3-7 x every 4-6 weeks</td>
<td>Median 35 (19-43) months</td>
<td>7/12</td>
<td>4 patient drop-outs due to personal reasons (n=1), pregnancy (n=1), relapse of intestinal symptoms (n=2)</td>
</tr>
<tr>
<td>Lorenzo-Zúñiga et al. (15)</td>
<td>Symptomatic isolated mucosal lesions</td>
<td>4</td>
<td>20-30 mg</td>
<td>1-3x, every 4 weeks</td>
<td>14-32 months</td>
<td>1/4 remission; 2/4 improved</td>
<td>1 patient remained in remission up to 32 months after 1 dose of 30 mg IFX</td>
</tr>
<tr>
<td>Swaminath et al. (20)</td>
<td>Colonic strictures</td>
<td>3</td>
<td>100-120 mg</td>
<td>1-5 doses with variable frequency</td>
<td>8-12 months</td>
<td>3/3</td>
<td>All participants were refractory to all medical therapy, including i.v. IFX; 1 patient also received manual dilation</td>
</tr>
<tr>
<td>Lichtiger et al. (1)</td>
<td>Perianal fistulas</td>
<td>9</td>
<td>20 mg</td>
<td>T=1, 2, 4, weeks</td>
<td>6 months</td>
<td>4/9 complete fistula healing; 3/9 improved</td>
<td>Autoantibodies against IFX (ATI) did not develop after 6-month follow-up</td>
</tr>
<tr>
<td>Hendel et al. (19)</td>
<td>Small bowel strictures</td>
<td>5</td>
<td>40 mg after endoscopic balloon dilatation</td>
<td>T=0, 2, 6 weeks</td>
<td>6 months</td>
<td>5/5 improved</td>
<td>all 5 patients at the final 6-month follow-up described relief of obstructive symptoms and no patients were referred to surgery during the follow-up period</td>
</tr>
</tbody>
</table>
regards to the efficacy. Furthermore, no data is available on the stability of IFX in the gastrointestinal tract of humans, of which the stability in the terminal ileum and colon is of particular importance for this study. However, the intraluminal pH of the terminal ileum and colon is generally not detrimental for proteins (pH 6-8).\textsuperscript{37-40} Finally, oral IFX therapy compliance may be challenging for some patients as they need to administer IFX daily and a dose can be forgotten, as opposed to infusion therapy.

There is no published data on the efficacious dose of oral ileo-colonic-targeted IFX. The total dose for every participant is therefore calculated in accordance with the intravenous dose of IFX divided by the treatment period in days.

**Methods/Design**

**Primary Objective:**
Primary objective of the study is to investigate the efficacy oral IFX biosimilar CT-P13 in ColoPulse tablets to induce clinical remission based on CDAI score of < 150 at week 18 in patient with active ileal or ileo-colonic CD.

**Secondary objectives:**
- Clinical response: CDAI reduction from baseline of ≥ 100 points
- Endoscopic remission: for patient with SES-CD of 3 a drop to 0 and for patient with SES-CD > 3 a drop ≤ 3
- Endoscopic response: proportion of subjects with SES-CD decrease from baseline of ≥ 50 % at Week 18 but not meeting criteria for endoscopic remission.
- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points at Week 18
- Number of patients with reduction in prednisolon dose below 10 mg or budesonide dose below 6 mg or off steroids at week 18.
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥10% at Week 18
- Improvement in faecal calprotectin and CRP level.
- IFX trough level at week 8 and 18
- Proportion of patients with development of antibodies to IFX CT-P13 at week 18
- Improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) scores
- Non-remitter: Subjects who do not achieves clinical remission at week 18
- Non responder: Subjects who do not achieve clinical response at Week 18.

**Study design**
This study will be a multicentre, open label, observational, proof of concept pilot study. The study will be performed at five sites in the north of the Netherlands (UMC Groningen, Isala Zwolle, MST Enschede, MCL Leeuwarden, Martini Hospital Groningen). In case of slow inclusion study can be extended to a nationwide ICC
study. The study consists of visits over 18 weeks. The total duration of drug treatment will be 18 weeks. In total, 12 subjects will receive the study drug.

**Patient population:**
Patients with active ileal or ileocolonic Crohn’s disease (CD). The aim is to enroll about 12 CD patients with refractory CD.

**Inclusion criteria**
- Male or female subjects aged 18 to 80 years at screening
- Subject must provide written informed consent prior to any study-related procedures, and have the ability to comply with the study procedures
- Subject has signs and symptoms consistent with a diagnosis of CD for at least 3 months (prior to first administration). The diagnosis should be confirmed by clinical and endoscopic evidence and supported by histology. CDAI score of > 220 and <450 and an average daily stool frequency ≥ 4 points and/or an abdominal pain of ≥ 2 points
- CRP >5 mg/L or Fecal calprotectin > 200 mg/kg.
- Has one or more ulceration on screening ileocolonoscopy which will result in an SES-CD total score of at least 3.
- Non active/non draining fistulas (including seton drained fistulas)
- Meets the following requirements for prior or current medications for CD:
  a) Has failed conventional therapy:
     i) Is currently receiving corticosteroids and/or immunomodulators (ie, thiopurine, MTX) at adequate therapeutic doses;
     OR
     ii) Has a history of failure to respond to, or tolerate, an adequate course of corticosteroids and/or immunomodulators (ie, thiopurine, MTX);
     OR
     iii) Is corticosteroid dependent or has a history of corticosteroid dependency;
     AND
  b) Has not previously received an approved biologic for CD (ie, IFX, adalimumab, certolizumab pegol, ustekinumab, natalizumab, vedolizumab or approved biosimilars of these agents)
- If the subject is taking the following background therapies for CD, a stable dose must be maintained before baseline as indicated below:
  - prednisone (doses ≤ 20 mg per day) or equivalent with a stable dose for at least 2 weeks prior to Screening endoscopy.
  - budesonide therapy (doses ≤ 9 mg per day) or beclomethasone doses ≤ 5 mg/day at a stable dose for at least 2 weeks prior to the Screening endoscopy.
Exclusion criteria

- Known history of other cause of colitis; e.g. ulcerative colitis, indeterminate colitis, microscopic colitis, ischaemic colitis or radiation-induced colitis, infectious colitis.
- Current abscess
- Symptomatic stricture or stenosis
- Subject is likely to require, in the physician’s judgment, bowel resection within 18 weeks of entry into the study.
- Abdominal, enterocutaneous or pelvic active fistulas or fistula likely to require surgery during the study.
- History of short bowel syndrome.
- Presence of ileostomy or colostomy.
- Previous use of anti-TNF alpha therapy.
- Prior primary efficacy failure of or secondary loss of response to anti-TNF-alpha therapy.
- Contra-indication to anti-TNF-alpha therapy.
- Positive result of tuberculosis surveillance.
- Presence of hepatitis B surface antigen (HBsAg), core antigen (HBCAg) or surface antibody (HBsAg), positive hepatitis C.
- Subject has documentation of a positive test for toxin producing Clostridium difficile (C. difficile), or polymerase chain reaction (PCR) examination of the stool on their most recent test, which must have been done in the past 60 days. If positive, subjects may be treated and retested no earlier than 7 days after completion of treatment.
- Subject has a history of active cancer within 5 years, including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or cervical dysplasia/cancer that have been excised and resolved); or colonic dysplasia that has not been completely removed.
- Oral antibiotics used for the treatment of Crohn’s disease.
- Subject has received a live or live attenuated vaccine within 4 weeks prior to the first dose of colopulse IFX
- Subject has chronic nonsteroidal anti-inflammatory drug (NSAID) use (note: occasional use of NSAIDs and acetaminophen [eg, headache, arthritis, myalgias, or menstrual cramps], aspirin up to 325 mg/day is permitted).

Permitted CD medications for the study are:

- Prednisone (doses ≤ 20 mg per day) or equivalent with a stable dose for at least 2 weeks prior to Screening endoscopy. Corticosteroids will be tapered by 5 mg per week.
- Budesonide therapy (doses ≤ 9 mg per day) or beclomethasone doses ≤ 5 mg/ day at a stable dose for at least 2 weeks prior to the Screening. Budesonide will be tapered by 3 mg per week.
- Subject has discontinued oral or rectal aminosalicylates.
- Methotrexate, thiopurines (ie azathioprine, 6-Mercaptopurine or Thioguanine).
Use of medication that can influence gastrointestinal pH, such as gastric antacids (calcium carbonate and the like), proton pump inhibitors (omeprazole, pantoprazole, and the like), and H2 antihistamine receptor antagonist (ranitidine and the like) are not allowed in this study.

**Dosages, dosage modifications and method of administration**

In this study we used CT-P13 IFX (a biosimilar). This biosimilar is proven to be as effective as its originator Remicade in vitro and in vivo.\(^1\) CT-P13 IFX 5 mg-sugar glass tablets coated with the ColoPulse technology are administered. No comparator or placebo is used during this study. Treatment consists of an oral daily dose in accordance with the intravenously administered dose of IFX, namely 5 mg/kg on day 0 with a repeated dose after 2 weeks (induction dose). Subsequently, another dose after 6 weeks of the first dose is given and thereafter a dose is administered every 8 weeks. This dose regimen is converted to a daily oral dosing regimen rounded to multiples of 5 mg evenly spread out over time. For example, if a participant of 80 kg were to receive one intravenous dose of 80 kg * 5 mg = 400 mg IFX in the first 2 weeks, then in this study the participant would receive 400 mg / 14 days = 30 mg oral IFX per day. A total daily dose equal to or greater than 10 mg is administered twice daily whereas a total daily dose of 5 mg is administered once daily. Table 3 summarizes the oral dosing regimen of this study.

**Study outline**

Table 4 shows the study outline. In brief, the demographic and baseline characteristics of interest include age, sex, smoking history, race/ethnicity, disease duration, extend and severity, extra intestinal complaints and (prior and concurrent) therapies (and results of those, and possible adverse events) for CD. Blood samples for hematology and serum chemistry panel and serum will be done in week 0, 2, 6, 14 and 18. Hematology sample will be drawn in the standard collection tube that is available at each investigational site. Hematology panel consists of: hemoglobin, hematocrit, red blood cell count, MCV, MCH, MCHC, WBC, differential, thrombocytes. These samples will be obtained in the standard collection tube that is available at each investigational site. Blood chemistry panel consists of: blood urea nitrogen (BUN), creatinine, total protein, albumin, total bilirubin (and direct bilirubin if total bilirubin is abnormally elevated), alkaline phosphatase, amylase, GGT, ALT, AST, sodium, potassium, and CRP. At week 0 blood samples will be taken for DNA research. This is for further research to identify and conform HLA regions associated with development of antibodies to IFX in IBD patients and to identify novel genetic regions associated with the development of ATI.\(^2\) At week 0, 2, 6, 14 and 18, the calprotectin level will be measured in the feces in the UMCG laboratory. The IFX trough level in sera will be measured at week 2, 6, 14 and 18 by an ELISA at Sanquin, Amsterdam.\(^3\) An colonoscopy will be performed.
at week 0 and week 18 to assess the severity of the inflammation (week 0) and to assess the response (by using the SES-CD score) of the treatment (week 18). At week 0, 2, 6, 14 and 18 the CDAI score will be calculated. The quality of life will be measured by the IBD-Q questionnaires at week 0 and week 18.

**Escape Medication**

Escape medication will be given in this study to patients who do not show response (CDAI reduction from baseline of ≥ 100 points at week 18). Escape medication is IFX CT P13 in the normal induction dose and scheme (5 mg/kg, 0-2-6 weeks and every 8 weeks thereafter). The same study parameters will be studied at week 18 after rescue medication inclusive the colonoscopy. It is possible that these patients are primary non responders and have to switch to another biological or other anti-TNF agents. This depends on the presence of antibodies to IFX that are measured in week 18.

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**Table 3.** The oral IFX dosing regimen of this study.

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>0-14</th>
<th>15-28</th>
<th>29-42</th>
<th>43-every 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily oral dose</td>
<td>(5 mg/kg) / 14</td>
<td>(5 mg/kg) / 14</td>
<td>(5 mg/kg) / 14</td>
<td>(5 mg/kg) / 56</td>
</tr>
</tbody>
</table>

**Table 4.** Study outline.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline information</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory diagnostics (Hb, leukocytes,</td>
<td>2</td>
</tr>
<tr>
<td>thrombocytes, CRP, albumin, AST, ALT, AF,</td>
<td>6</td>
</tr>
<tr>
<td>GammaGT, bilirubin, urea, creatinin)</td>
<td>14</td>
</tr>
<tr>
<td>Blood for DNA analysis</td>
<td>18</td>
</tr>
<tr>
<td>Faeces calprotectin</td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td></td>
</tr>
<tr>
<td>CDAI/HBI</td>
<td></td>
</tr>
<tr>
<td>S IBD Q</td>
<td></td>
</tr>
<tr>
<td>IFX level</td>
<td></td>
</tr>
<tr>
<td>Antibodies to IFX</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Collect stool</td>
<td></td>
</tr>
<tr>
<td>Collect serum</td>
<td></td>
</tr>
</tbody>
</table>

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TOMATE: a proof of concept study

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Data Analysis

Sample size
This is an open label proof of principle study. No formal statistical hypothesis testing will be performed for this study. Descriptive statistics and 95% confidence intervals will be employed where appropriate for data analysis. The sample size for this study was determined to account for the variability within the heterogeneous group of CD and is not based on statistical power calculation. In the first IFX placebo controlled trial with 5 mg/kg IFX clinical response and clinical remission at 12 weeks was 48% and 30% and the placebo response and remission 12% and 8% respectively. In the phase 3 SONIC trial, which compares IFX 5 mg/kg monotherapy to combination therapy with Azathioprine, remission rates defined as CDAI <150-points, clinical response defined as >100-point decrease in CDAI from baseline and clinical response defined as >70-point decrease in CDAI from baseline in the IFX monotherapy arm at Week 18 were 49.7%, 55% and 60.9% respectively. IBDQ and CRP change from baseline at week 18 were 39.9 and -1.3 (mean ± SD) respectively. The percentage responders at 18 weeks is expected to be 20% higher than the placebo response rate of 12% and placebo remission rate of 8%. A fully sequential design with continuous monitoring of response will be used. A total of 39 patient is needed to show efficacy. The efficacy is scored according to clinical response (CDAI reduction from baseline of ≥ 100 points and of ≥ 70 points) and clinical remission efficacy criteria. In case one or more of these efficacy criteria is achieved this will be called an “event”, and these events will be plotted in a diagram (Figure 1). In case the event line passes the green line (event rate will be < 32%) the study will be discontinued.

![Stopping Rule Diagram](image-url)
Primary Endpoint
The between-group difference in the primary outcome will be analyzed using the Chi square test of Fisher exact test when appropriate.

Secondary endpoint
With regard to the secondary endpoints reflecting ‘time to event’. We will compute survival curves (time-to-event analysis) for both groups using the Kaplan-Meier methodology. Significance of differences between curves will be calculated using the log-rank test.
The remaining secondary outcomes will be analyzed using the appropriate parametric or non-parametric techniques (two group t-test, Mann-Whitney U test, Chi-square test or Fisher exact test).

Safety monitoring and ethics
This research will be conducted according to the principles of the Declaration of Helsinki Fortaleza (Brasil) in 2013 in accordance with the Medical Research Involving Human Subjects Act (WMO) (Wet Medisch Wetenschappelijk onderzoek met mensen). Written informed consent will be obtained from patients before inclusion in the trial.

All adverse events (AE), whether or not considered related to the oral IFX, will be registered. Moreover, serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the accredited Medical Ethical Committee (MEC).

The risk of this study is considered ‘low’ because of IFX is an common used drug.

An independent data and safety monitoring board (DSMB) will examine safety parameters and evaluate the overall progress of the trial. The DSMB will consist of an epidemiologist/statistician who is the chairman, an independent surgeon and an independent internist. The responsibilities of the DSMB are to monitor safety data when 50% of the patients have been randomized and, if required, on ad hoc basis. Any mortality will be reported directly to the DSMB and evaluated for cause of death and possible trial related serious adverse events.

The justifications for a recommendation to terminate the study due to clear harm will be based on a notably increase of (serious) adverse events. Statistical stopping boundaries will not be pre-specified.

The advice(s) of the DSMB will only be sent to the principal investigator of the study. Should the principal investigator decide not to fully implement the advice of the DSMB, the principal investigator will send the advice to the reviewing MEC; including a note to substantiate why (part of) the advice of the DSMB will not be followed.
Discussion/Potential implications

IFX has been proven to be effective in the treatment of CD and is effective in induction and maintaining remission of CD.\textsuperscript{5,46} It is administered intravenously at doses based on weight and fixed intervals. Previous studies showed that local treatment with IFX is efficacious like topic IFX injection for rectal stenosis in CD patients.\textsuperscript{47} Also in other studies where local IFX was administered is was proven to be effective (table 2).\textsuperscript{38-36} Additionally, topical IFX treatment presumably results in a continuous IFX exposure at the site of inflammation with fewer side effects compared to systemically administered IFX. The development of a subcutaneous formulation of CT-P13 IFX for rheumatoid arthritis is described.\textsuperscript{48} These patients had more stable steady state therapeutic blood levels of IFX and have lower rate of ATI compared with patients receiving continued IFX IV treatment. More recently in IBD patients also efforts has been made to use subcutaneous IFX. Preliminary results suggest that one year treatment with subcutaneous CT-P13 IFX is similar in efficacy and safety compared to intravenous administration in CD patients.\textsuperscript{49} There are gut specific oral agents in treatment of IBD like slow release mesalazine and budesonide. These drugs are proven to be effective in IBD. Beside these there are local acting drugs like mesalazine suppositories, mesalazine enemas and beclometason/budesonide suppositories and enemas. Several oral targeted therapies are in development.\textsuperscript{50} Efficacious oral anti-TNF alpha or IFX treatment has major advantages for patients with CD. First, patients no longer need to visit the hospital for medical treatment. Second, patients will not be punctured by for infusion therapy and also the personnel do not have to receive a training for the procedure. Third, oral treatment eliminates infusion quality of life influencing related complications, such as extravasations and infusion reactions. Finally, local treatment of anti-TNF-alpha reduces the risk of developing of antibodies to the anti-TNF-alpha containing agent. An oral administration of the non-absorbable recombinant anti-TNF-alpha fusion protein, PRX-106 has been shown to be safe, not associated with immune suppression, while inducing a favorable anti-inflammatory immune modulation in healthy volunteers.\textsuperscript{51} A novel polyclonal anti alpha antibody (AVX470) was effective in treating mouse models of colitis, delivering the anti-TNF to the site of inflammation with minimal systemic exposure.\textsuperscript{52} Another novel anti-TNF alpha domain antibody (V565) could be detected by ELISA in post-dose serum of colitis mice, but not in naïve mice, demonstrating penetration of disrupted epithelium.\textsuperscript{53} An open label study in ulcerative colitis demonstrated binding to CD14 +macrophages in the lamina propria of UC patients and resulted in inhibition of mucosal inflammatory processes after 6–7 days oral dosing.\textsuperscript{54} The colopulse capsule is specifically developed to target the ileo-colonic region. This local administration is therefore ideal for CD patients with active disease of the terminal ileum. The clinical response and endoscopic response are both important at week 18. Of interest, The Mongerson trial which showed that patients with CD who received oral Mongersen targeting SMAD7, an inhibitor of cytokine transforming growth factors β1 (TGF-β1), had significantly higher rate of remission and clinical response than those who received placebo.\textsuperscript{55} However, in a follow-up phase III study the trial was ended due
to futility. Some important limitations of the phase II trial were addressed in the accompanying editorial. The inclusion criteria of the phase II study did not include objective criteria for active disease such as endoscopic confirmation of inflammation, but were only based on CDAI score. It is therefore unclear what proportion of these patients had mucosal lesions. Additionally, 40% of the patients did not have an increased level of CRP at baseline or had a normalization of CRP during the study period. Therefore the clinical remission and biological remission were not in correspondence, a conclusion supporting the later futility of the phase III trial. To overcome this problem our protocol has the advantage that IFX has been used for many years in CD patients and therefore has proven efficacy and safety profile. Additionally, our protocol includes monitoring of disease activity by CDAI score (for clinical response) as well as objective measurements such as CRP, fecal calprotectin and endoscopic response at week 18. This allows us to combine clinical and endoscopic response as a valid primary outcome for CD patients. In conclusion, there is a rationale for a trial with topical IFX delivered with the colopulse technology. If proven efficacious, oral IFX therapy could lead to a more patient tailored therapy of IFX and reduce health care costs and patient burden.
Chapter 10

References


